RESEARCH PAPER

Vitamin D Supplementation for Severe Pneumonia – *A Randomized Controlled Trial*

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Objective: To determine the role of oral vitamin D supplementation for resolution of severe pneumonia in under-five children.

Design: Randomized, double blind, placebo-controlled trial.

Setting: Inpatients from a tertiary care hospital.

Participants: Two hundred children [mean (SD) age: 13.9 (11.7) months; boys: 120] between 2 months to 5 years with severe pneumonia. Pneumonia was diagnosed in the presence of fever, cough, tachypnea (as per WHO cut-offs) and crepitations. Children with pneumonia and chest indrawing or at least one of the danger sign (inability to feed, lethargy, cyanosis) were diagnosed as having severe pneumonia. The two groups were comparable for baseline characteristics including age, anthropometry, socio-demographic profile, and clinical and laboratory parameters.

Intervention: Oral vitamin D (1000 IU for <1 year and 2000 IU for >1 year) (*n*=100) or placebo (lactose) (*n*=100) once a day for 5 days, from enrolment. Both the groups received antibiotics as per the Indian Academy of Pediatrics guidelines, and supportive care (oxygen, intravenous fluids and monitoring).

Outcome variables: *Primary*: time to resolution of severe pneumonia. *Secondary*: duration of hospitalization and time to resolution of tachypnea, chest retractions and inability to feed.

Results: Median duration (SE, 95% CI) of resolution of severe pneumonia was similar in the two groups [vitamin D: 72 (3.7, 64.7-79.3) hours; placebo: 64 (4.5, 55.2-72.8) hours]. Duration of hospitalization and time to resolution of tachypnea, chest retractions, and inability to feed were also comparable between the two groups.

Conclusion: Short-term supplementation with oral vitamin D (1000-2000 IU per day for 5 days) has no beneficial effect on resolution of severe pneumonia in under-five children. Further studies need to be conducted with higher dose of Vitamin D or longer duration of supplementation to corroborate these findings.

Key words: *ARI, India, Pneumonia, Treatment, Vitamin D.*

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Pneumonia is one of the leading causes of childhood mortality worldwide; accounting for nearly one-fifth of the under-five deaths in India [1]. Besides antibiotics, zinc and vitamin A have been suggested to have beneficial role in children with severe pneumonia [2-5]. Recent research indicates that Vitamin D may have a potential role in protection from acute respiratory tract infections by increasing the body's production of naturally acting antibiotics [6]. Vitamin D has also been found to have immune modulating properties by virtue of its ability to induce monocyte differentiation and inhibit lymphocyte proliferation [6-10]. Vitamin D has antimicrobial properties as it stimulates phagocytosis-dependent and antibody-dependent macrophages [6]. 1,25-dihydroxy vitamin D_3 also acts upon T and B cells and can modulate functions of lymphocytes that produce cytokines and antibodies [8]. Severe deficiency of vitamin D leads to chest wall deformity and hypotonia, leading to reduced lung volume, poor compliance of the chest wall, atelectasis and fibrosis [11]. An Ethiopian study has found a 13-fold higher incidence of severe vitamin D deficiency in children with pneumonia, as evident clinically by presence of rickets [12].

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Despite evidence for a positive correlation between vitamin D deficiency and incidence of pneumonia [11], data regarding the direct effect of vitamin D supplementation in acute attacks of pneumonia is limited to only one study [13]. We conducted this trial to test our hypothesis that vitamin D supplementation decreases the duration of resolution of severe pneumonia in children under five years of age.

METHODS

A double blind, randomized, placebo-controlled trial was

conducted in children between 2 months and 5 years admitted with a diagnosis of severe pneumonia in a tertiary care hospital. Permission was obtained from the institutional ethical committee and written informed consent obtained from the caregiver of the participant.

Enrolment: The sample size was based on a hospital based randomized control trial on the role of zinc for severe pneumonia in very young children [3]. A total of 98 patients were required in each group to detect a meaningful difference of one day in resolution of severe pneumonia with standard deviation of 2.5, type 1 α error 0.05 and power of 80%. Eligible subjects included all children between 2 months – 5 years with a clinical diagnosis of severe pneumonia, presenting to pediatric emergency department. Children with fever, cough, tachypnea and crepitations were diagnosed with pneumonia. Tachypnea was defined as respiratory rate ≥50/min in children between 2-12 months and ≥40/min in 1-5 years age group [14]. Those with pneumonia and either chest indrawing or at least one other danger sign (inability to feed, lethargy, and cyanosis) were diagnosed as having severe pneumonia. Children with severe wasting (weight for height <3SD), chronic illnesses, previous history of vitamin D intake over last 4 weeks, and known asthmatics were excluded.

Randomization and blinding: Randomization was done according to computer generated random number table. Allocation concealment was done by sealed envelope technique. Both the caretaker and subject were blind regarding the content of the drug been given. Each sachet of vitamin D contained 1000 IU of drug whereas the placebo sachet contained lactose. One sachet of vitamin D (60,000 IU) weighing 1g was mixed with 11 gm of lactose, total weight being 12g. Of this, 60 doses were taken each weighing 200 mg so that each dose carried 1000 IU of vitamin D. Both looked alike in terms of appearance, taste and color. The code key was opened only after the intervention, data collection, follow up and tabulation were completed.

Initial data collection: A detailed history (including socio-demographic profile, feeding history, immunization, past history of pneumonia, fuel use or smoking) was taken and clinical examination (including anthropometry as per tools and standard techniques) [15] was performed for each of the participant. Respiratory rate were counted for full 60 seconds, after removing all clothes from the torso and also chest indrawing was observed at the same time. Average of two readings was recorded. If the readings differed by more than 5 breaths per minute, a third reading was taken and the two closest readings averaged. Child had to be awake and not crying during these measurements. Axillary temperature was taken with a standardized mercury thermometer. Fever was defined as temperature >38ºC. Baseline oxygen saturation was measured in room air using a pulse oximeter with a probe on a finger or toe. Hypoxia was defined as oxygen saturation <95% in room air [3]. Weight and height were measured using standard techniques. Venous blood sample was obtained for hemogram, blood sugar, electrolytes, C-reactive proteins (latex slide test, >0.8mg/dL taken as positive), calcium, phosphate and alkaline phosphatase. All data including respiratory rate, retractions, oxygen saturation, fever, feeding, cyanosis and mental status were recorded.

Intervention: Children were randomized to receive either vitamin D or placebo as a single oral dose every day, for five days from enrollment. Authors were not involved with the randomization process. Vitamin D was given as 1000 IU to children less than one year old and 2000 IU children between 1-5 years of age. The drug/placebo was dispensed in milk and administered orally within four hours of admission. This was followed by once-a-day dosing for next 4 days. Those unable to take orally were given the drug by nasogastric tube. The drug was repeated if an episode of vomiting occurred within 15 minutes of ingestion of drug. Both the groups received antibiotics as per Indian Academy of Pediatrics (IAP) guidelines [16] and supportive care (oxygen, intravenous fluids and monitoring). Children with associated wheezing received salbutamol nebulization twice at an interval of 20 minutes.

Clinical monitoring: Data including respiratory rate, retractions, oxygen saturation, fever, feeding, cyanosis and mental status were recorded every 8 hourly. Worsening of any one sign was qualified as 'deteriorating' condition and no change in any sign as failure to improve. Child was reclassified from severe pneumonia to pneumonia (non severe) when chest indrawing and hypoxia (saturation less than 95% on room air) were absent for 24 consecutive hours and respiratory rate was less as per age cut off, at which oral antibiotic was started. Oral feeding was also started at this point of time. If any signs recurred, the child was reclassified as severe until these conditions were met. All children received a minimum of 5 days of IV/oral antibiotics. Children were discharged when tachypnea had subsided for a minimum of 24 hours. Subjects with clinical rickets were given a mega dose of vitamin D (6,00,000 IU) at the time of discharge. All children were observed for adverse effects and compliance.

Primary outcome variable: The primary outcome of interest was the time to resolution of severe pneumonia.

Resolution of severe pneumonia was considered when lower chest retraction and the danger signs (inability to feed, lethargy, cyanosis or hypoxia) were no longer present.

Secondary outcome variables: The secondary outcome variables included the duration of hospitalization, and time to resolution of tachypnea (respiratory rate cut off for severe pneumonia as per age), chest retractions, and inability to feed. The duration of hospitalization was defined as the time (in hrs) between study enrolment and discharge. The patient was considered fit for discharge when he/she was afebrile (axillary temperature <37.5ºC), tachypnea had subsided, there were no chest indrawings, and oral feeding had resumed, for a minimum period of 24 hours.

Statistical analysis: Baseline characteristics between the two groups were compared using chi-square/Fisher's test for categorical variables and unpaired *t* test for quantitative variables, as these were normally distributed. The effect of vitamin D supplementation on outcome variables was analyzed on intention to treat basis. Kaplan Meier survival function plots were constructed to compare median duration of each outcome variable between the two groups using the log rank test. $P < 0.05$ was taken as significant. The data were analyzed by using SPSS software.

RESULTS

Overall, 283 children were diagnosed with severe pneumonia during the study period, of which, 200 were randomized (***Fig.* 1**). The median (IQR) age of study subjects was 10 (5-18) months. Number of children below 2 years was comparable in the two groups (vitamin D: 84; placebo: 85). The two groups were also comparable for other baseline characteristics including socio demographic profile, anthropometry, and clinical and laboratory parameters (***Table* I** and **II**). Only 5 children had clinical evidence of rickets; 2 in vitamin D and 3 in placebo group. Fever, cough, coryza, irritability and decreased oral acceptance were seen in all patients admitted and enrolled for the study. The median (IQR) duration of illness at presentation was 5 (4-7) days. Wheeze was present in almost 1/3rd of the subjects (33.5%); 32 children in vitamin D group and 35 in placebo group. Cyanosis was not present in any case on presentation. The mean oxygen saturation was 92.8% ± 2.4. C-reactive protein (CRP) was positive in 161/197 cases (81.7%). Of these, 82 cases were in vitamin D group and 79 cases in the placebo group.

The median duration for resolution of severe pneumonia and hospitalization was comparable in the two groups (***Fig* 2*a*, 2*b***). The two groups were also comparable for time taken for resolution of tachypnea,

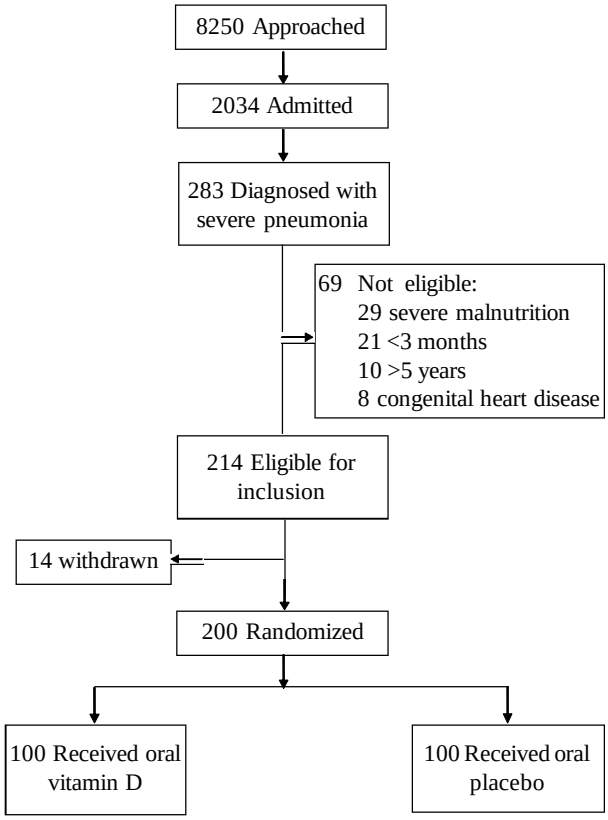

FIG. 1 *Flow chart depicting the inclusion of the study subjects.*

TABLE I BASELINE CHARACTERSTICS OF THE STUDY POPULATION

Parameter	*Vitamin D n (%)*	*Placebo n (%)*
Socioeconomic status		
Upper	0	0
Upper middle	10 (10%)	4 (4%)
Lower middle	22 (22%)	23 (23%)
Upper lower	66 (66%)	72 (72%)
Lower	2 (2%)	1 (1%)
Residence		
Urban	24 (24%)	19 (19%)
Rural	29 (29%)	34 (34%)
Slum	47 (47%)	47 (47%)
Passive smoking	28 (28%)	30 (30%)
Use of wood /coal / kerosene	28 (28%)	32 (32%)
Immunization		
Complete	51 (51%)	38 (38%)
Partial	34 (34%)	37 (3%)
Unimmunized	15 (15%)	25 (25%)
Past history of pneumonia	30 (30%)	33 (33%)
History of TB contact	1 (1%)	0

TABLE II BASELINE CHARACTERISTICS, ANTHROPOMETRY, VITAL SIGNS AND LABORATORY PARAMETERS IN THE VITAMIN D VERSUS PLACEBO GROUP

Parameters	*Vitamin D (Mean±SD)*	*Placebo (Mean±SD)*
Age (mo)	14.1±12.2	13.8±11.4
Weight (kg)	7.5±2.5	7.3±2.7
Length (cm)	70.0±10.6	70.1±11.9
Head circumference (cm)	44.6±3.2	44.3±3.7
Chest circumference (cm)	44.6±4.1	44.4±4.2
Mid-arm circumference (cm)	11.2±1.4	11.1±1.4
Breastfeeding* (mo)	7.7±5.8	8.5±5.9
Exclusive breastfeeding* (mo)	3.9±1.7	3.9±2.4
Complementary feeding# (mo)	7.8±2.0	8.7±2.3
Respiratory rate (breaths/min)	69.2±9.1	68.2±8.9
SpO_2	92.8±2.6	92.9±2.3
Hemoglobin (g/dL)	9.3±1.7	9.0±1.5
TLC (/cumm)	11938.6±5320	12910±6640
S. Calcium (mg/dL)	9.2±0.81	9.2±0.75
S. Phosphorus (mg/dL)	5.1±1.4	5.3±1.8
S. ALP (IU/L)	292.6±136.7	356.1±244.7

** Duration; #Age at initiation of*

chest retractions, hypoxia, fever, inability to feed and lethargy/irritability (***Table* III)**.

A total of 140 children (vitamin D 68, placebo 72) received first line antibiotics, whereas in 60 children, second line antibiotics had to be started. Of those who received second line antibiotics, 32 children were in vitamin D group and 28 in placebo group. Staphylococcal coverage was given in 25 children, of which 18 were in vitamin D group and 7 in placebo group. Of 200 children, 97 children in vitamin D group and 94 children in placebo group were finally discharged. Of the 191 children discharged, 28 children (11 vitamin D, 17 placebo) were discharged within 72 hrs, 95 (47 vitamin D, 48 placebo) were discharged between 72-120 hrs while 65 children (34 vitamin D, 31 placebo) were discharged after 120 hours of hospitalization.

Overall 173 (86.5%) children improved (vitamin D: 87; placebo: 86) and 23 (11.5%) remained in the same condition. Worsening occurred in 4 (2%) children only. Two children died, 1 each in vitamin D and placebo group. A total of 7 children could not complete the study as parents left against medical advice (***Fig.* 1**). There was no difference between the two groups in the proportion of children who improved.

A total of 191 children received all five doses of the drug. No major adverse effects were noted. Only one child had a single episode of vomiting and another complained of diarrhea that lasted two days. Both the children belonged to the vitamin D group.

DISCUSSION

The results indicate that short-term supplementation with vitamin D does not decrease the duration of resolution of severe pneumonia, duration of hospitalization, and time taken for resolution of individual symptoms of severity of pneumonia in under-five children. Vitamin D supplementation was well tolerated in all age groups without showing any major side effects. These results are important; however, they need further deliberations. Our study has certain limitations and thus it may not be justified to generalize the results to all acute lower respiratory tract infection at all ages and all settings.

Due to safety concerns, we kept the doses in our study lower than the No Observed Adverse Effect Level (NOAEL; 2400IU) and Lowest Observed Adverse Effect Level (LOAEL; 3800 IU) [17]. A higher dose was not administered because of lack of safety data in children and absence of vitamin D level monitoring. It is possible that a larger dose is required to demonstrate the therapeutic effects of vitamin D in infection. Initially it was thought that people living in areas with poor sun exposure are affected but now there is evidence that vitamin D deficiency is rampant even in tropical countries. Mothers and their breast fed infants have also been found to be severely deficient in vitamin D [18]. Thus it may be possible that the recruited children were already deficient in vitamin D and our doses were too less to cause an impact. This could have been avoided by measuring vitamin D levels but due to financial constraints, the levels could not be checked and hence, we could not categorize the therapeutic effect separately for vitamin D replete and deplete subjects. Previous studies have also shown that after receiving single large doses, some of the cases took nearly 2 months for the peak concentration to be achieved [19]. Thus it could be possible that with the daily doses given in our study, the blood levels of vitamin D might still be sub-optimal for the effects to occur.

We could not find any trial that evaluated the therapeutic role of daily supplementation of vitamin D in severe pneumonia. Only a single trial till now has ascertained the role of vitamin D in pneumonia which studied 453 children, of which 224 children received single dose of 100,000 IU of oral vitamin D and 229 children received placebo. No significant difference was noted in the duration of recovery from severe pneumonia, but recurrence was lower in vitamin D supplemented group within 90 days of supplementation [13].

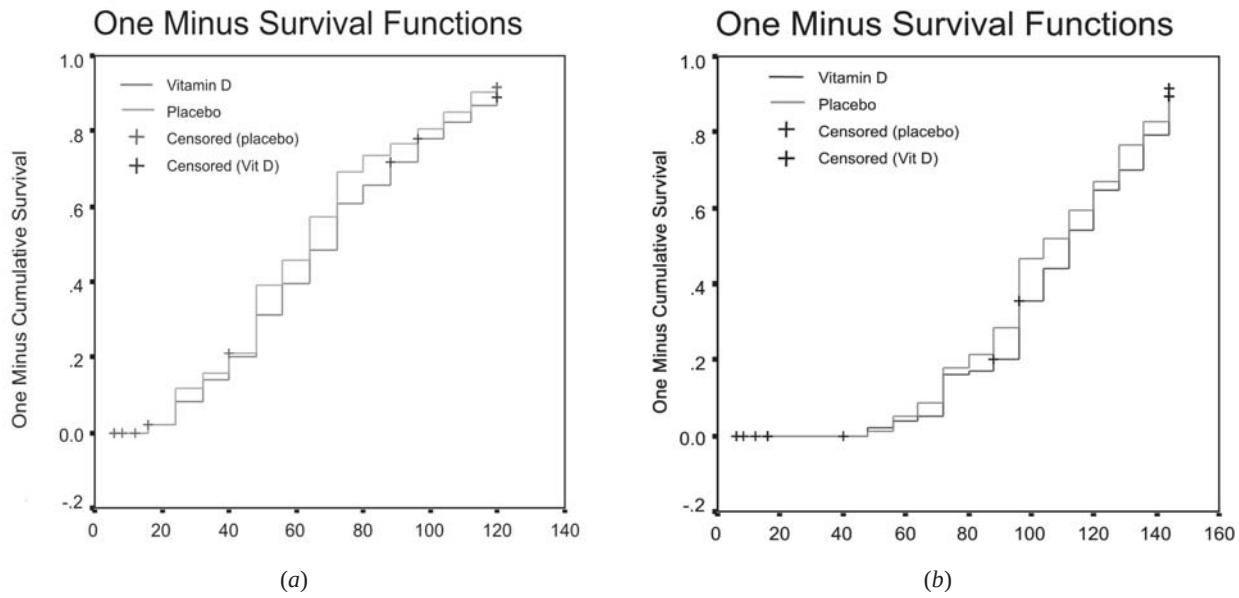

FIG. 2 *(a) Time to resolution of severe pneumonia (hours); (b) Duration of hospitalization (hours).*

We conclude that short-term supplementation with 2000 IU of vitamin D given orally for five days in severe pneumonia to under-five children has no beneficial effect on resolution of severe pneumonia. However, further studies needs to be conducted with higher doses of vitamin D and longer duration of supplementation and follow-up, to ascertain the therapeutic as well as prophylactic role of vitamin D for childhood pneumonia. Vitamin D estimation also needs to be done and the response segregated for vitamin D deplete and replete children.

Contributors credit: NC: Collected the data and wrote the initial manuscript; PG: designed the study, searched the literature and critically analyzed the data and manuscript. Both authors approved the final manuscript.

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TABLE III RESOLUTION OF SYMPTOMS (HOURS) IN VITAMIN D AND PLACEBO GROUP

	Vitamin D		*Placebo*		**P value*
	n	*Median (IQR)*	*n*	*Median (IQR)*	
Resolution of					
Severe pneumonia (h)	87	72 (48-96)	86	64 (48-88)	0.33
Tachypnea (h)	87	72 (56-104)	84	72 (48-98)	0.33
Chest retractions (h)	87	64 (40-88)	86	64 (40-88)	0.38
Hypoxia (h)	87	16 (8-24)	86	16 (8-24)	0.86
Fever (h)	87	80 (64-104)	85	72 (56-104)	0.52
Inability to feed/lethargy (h)	87	64 (48-88)	86	56 (48-72)	0.21
Duration of hospitalization (h)	87	112 (96-136)	86	104 (88-128)	0.29

**Group comparison done with survival analysis using log-rank test.*

WHAT IS ALREADY KNOWN?

- Vitamin D deficiency predisposes to infections; vitamin D acts as immune modulator.

WHAT THIS STUDY ADDS?

- Vitamin D supplementation at doses of 1000 IU and 2000 IU for children <1 year and > year, respectively given daily for 5 days has no beneficial effect in severe pneumonia.

prevention of childhood diarrhea and respiratory illness: A meta-analysis. Pediatrics. 2007;6:1120-30.
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